Heterogeneity of the Psychoses: Is There a Neurodegenerative Psychosis?

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Abstract

Whereas etiological heterogeneity of the various types of schizophrenia has been repeatedly proposed, relatively few attempts have been made to separate the component diseases. Using a strategy focusing on bimodal distributions within several relevant domains of schizophrenia, we demonstrate that currently available data on schizophrenia patients are consistent with the hypothesis that some of these patients have an ongoing neurodegenerative disease, whereas others do not. We review studies (longitudinal and cross-sectional) documenting progressive increases in ventricular size, accelerated loss of brain tissues, progressive delays in treatment response, and neurochemical (magnetic resonance spectroscopy) and neurophysiological (P300) indices, all of which are consistent with ongoing cerebral degeneration in a significant subgroup of schizophrenia patients. These lines of evidence converge on a conceptualization of schizophrenia as being composed of several etiologically distinct processes, with one subset of psychotic patients evidencing progressive brain degeneration. We conclude with a discussion of possible etiologies for this condition.

Key words: Heterogeneity, ventricular brain ratio, phosphoesters, evoked cortical response, degeneration, apoptosis, drug response.

***Schizophrenia Bulletin*, 24(3):365–379, 1998.**

A growing body of evidence indicates that schizophrenia is not a single disease, but is composed of several etiologically distinct processes that give rise to the hallucinations, delusions, disordered thought processes, and the volitional defects characteristic of the syndrome. This concept of heterogeneity has been frequently entertained in the last decade (Crow 1982; Goetz and van Kammen 1986; Pandurangi et al. 1989; Chang et al. 1990, 1993; Peralta et al. 1992; Pulver et al. 1995; Wang et al. 1995). However, few investigators have rigorously attempted to separate the proposed etiologic heterogeneity of schizophrenia into its component parts. If schizophrenia is itself an admixture of several different disease processes, the data derived from most cohorts of schizophrenia subjects must also reflect an admixture of several disease processes. A particularly relevant clinical or biological finding concerning one of the disease processes in such a mixed cohort may thus be obscured by the presence of other psychotic disorders not possessing the abnormality of interest. Detection and specification of one of the diseases is often the result of studying a cohort of patients particularly enriched in a single disease (Garver et al. 1997).

We previously provided preliminary evidence from drug response studies (Garver et al. 1988) that the "Group of the Schizophrenias" is an admixture of psychotic disorders. The group consists of both familial (presumably genetic) diseases (Kety et al. 1976) and environmentally-induced phenocopies, some of which may be caused by neurotropic viruses or other risk factors (Edelman and Chuong 1982; Mednick et al. 1988; Hollister et al. 1996; Susser et al. 1996). There is growing evidence for at least three forms of familial schizophrenia: an already well-documented early "neurodevelopmental" disorder (Conrad and Scheibel 1987), a "dopamine psychosis" (resulting from excess synaptic dopamine) found in good-prognosis psychotics (Garver et al. 1997), and a third familial psychosis which we now describe, a "neurodegenerative psychosis." Neurodegenerative psychosis results from an active, ongoing degenerative process especially prominent during the late teens and early twenties, continuing throughout adult life.

To support this proposition, we selected reports using data most relevant to neurodegeneration: accelerated

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increases of cerebral ventricular size, premature (age-related) loss of brain substance, progressive delay in treatment response, evidence of premature dementia, and neurochemical and neurophysiological changes. When viewed as a whole, the results of these studies support the concept of neurodegeneration in one subgroup of schizophrenia patients. We then review possible directions for research into the etiologies of the neurodegenerative process.

Studies Supporting a Neurodegenerative Psychosis

Progressive Increase in Ventricular Size in Schizophrenia. Increasingly sophisticated brain-imaging techniques (pneumoencephalography, computerized axial tomography [CAT], and magnetic resonance imaging [MRI]) have shown that a substantial number of young adults with schizophrenia have cerebral ventricular enlargement that cannot be accounted for by substance abuse, trauma, or other known causes of brain atrophy (for a review, see Coffman 1989). The critical question is whether such cerebral ventricular enlargement is a consequence of some early neurodevelopmental event and is thus static in adulthood, or whether such enlargement is ongoing and progressive during the course of the illness. If, in an adult with schizophrenia, the size of the ventricles progressively increases as the illness progresses at a rate in excess of that found in controls, an active progressive degenerative process (as opposed to a now static early neurodevelopmental abnormality) can be reasonably proposed.

Reanalysis of Longitudinal Studies of Cerebral Ventricular Size. Serial (within-subject) ventricle-to-brain ratios (VBRs) of schizophrenia subjects were selected from the literature. To assess age-related effects on changes in ventricular size, only studies that included the patient's age at index scan (rather than mean ages for groups of patients) and demonstrated an error for the VBR method of less than ± 1 VBR unit (see below) were included in the analysis. Four studies involving a total of 44 schizophrenia patients and 8 controls qualified for inclusion (Kemali et al. 1989; Woods et al. 1990; Jaskiw et al. 1994; Vita et al. 1994). To compensate for the varying intervals between index and subsequent scans (1 to 6 years), each patient's VBR was standardized by multiplying the total VBR change by 24 months and dividing by the number of months between scans to yield the VBR change per 24 months. VBR data for each subject in the four studies are listed in table 1.

The "error of the method" in VBR assessments can result from various factors. For example, the maximum

Table 1. Age and ventricle-to-brain ratio (VBR) data from four studies examining serial (within-subject) VBRs of schizophrenia subjects, involving a total of 44 schizophrenia patients and 8 controls

	Age	Initial VBR	Subsequent VBR	Months between VBRs	Change in VBR	VBR change per 24 months
Kemali et al. 1989						
Schizophrenia subjects	26	3.8	3.4	37	–0.4	–0.27
	21	2.0	2.0	37	0	0
	36	5.8	5.0	37	–0.8	–0.53
	31	1.3	4.2	37	+2.9	+1.93
	39	5.2	5.7	37	+0.5	+0.33
	29	4.3	4.3	37	0	0
	32	7.4	8.2	37	+0.8	+0.53
	27	2.8	3.0	37	+0.2	+0.13
	36	2.0	3.6	37	+1.6	+1.07
	31	4.5	4.9	37	+0.4	+0.27
	16	4.8	5.4	37	+0.6	+0.04
	24	5.3	5.1	37	–0.2	–0.13
	25	3.8	3.5	37	–0.3	–0.20
	26	1.3	4.0	37	+2.7	+1.80
	37	3.3	5.6	37	+2.3	+1.53
	20	1.2	1.6	37	+0.4	+0.27
	27	1.5	1.6	37	+0.1	+0.07
	21	6.4	5.7	37	–0.7	–0.47
Controls	33	2.0	1.8	37	–0.2	–0.13
	35	4.8	4.9	37	+0.1	+0.06
	19	2.3	2.3	37	0	0

Table 1. Age and ventricle-to-brain ratio (VBR) data from four studies examining serial (within-subject) VBRs of schizophrenia subjects, involving a total of 44 schizophrenia patients and 8 controls—*Continued*

	Age	Initial VBR	Subsequent VBR	Months between VBRs	Change in VBR	VBR change per 24 months
	18	1.9	1.7	37	–0.2	–0.13
	36	1.4	1.5	37	+0.1	+0.06
	36	2.0	1.8	37	–0.2	–0.13
	32	3.3	3.2	37	–0.1	–0.06
	25	1.9	2.1	37	+0.2	+0.13
Woods et al. 1990						
Schizophrenia subjects	25	3.8	6.9	24	+3.1	+3.10
	23	7.1	8.0	30	+0.9	+0.72
	20	7.3	13.4	20	+6.1	+7.32
	27	8.2	9.1	12	+0.9	+1.80
	31	11.7	15.0	42	+3.3	+1.89
	20	12.8	19.1	30	+6.3	+5.04
	20	15.2	18.4	48	+3.2	+1.60
	24	15.8	18.2	24	+2.4	+2.40
	37	7.6	7.3	36	–0.3	–0.20
Jaskiw et al. 1994						
Schizophrenia subjects	31	6.2	5.8	72	–0.04	–0.13
	17	14.0	11.2	72	–2.8	–0.93
	39	2.6	7.3	72	+4.7	+1.57
	20	10.2	8.2	72	–2.0	–0.67
	31	8.0	7.0	72	–1.0	–0.33
	32	2.0	0.6	72	–1.4	–0.47
	14	6.0	6.8	72	+0.8	+0.27
	19	10.2	10.2	72	0	0
Vita et al. 1994						
Schizophrenia subjects	18	1.1	1.0	24	–0.1	–0.10
	21	2.1	1.7	30	–0.4	–0.32
	19	3.7	2.1	36	–1.6	–1.07
	25	8.0	7.7	32	–0.3	–0.23
	28	9.4	9.2	28	–0.2	–0.17
	19	5.9	6.1	24	+0.2	+0.20
	18	6.6	7.2	24	+0.6	+0.60
	32	9.0	9.4	26	+0.4	+0.37
	21	8.8	9.0	46	+0.2	+0.10

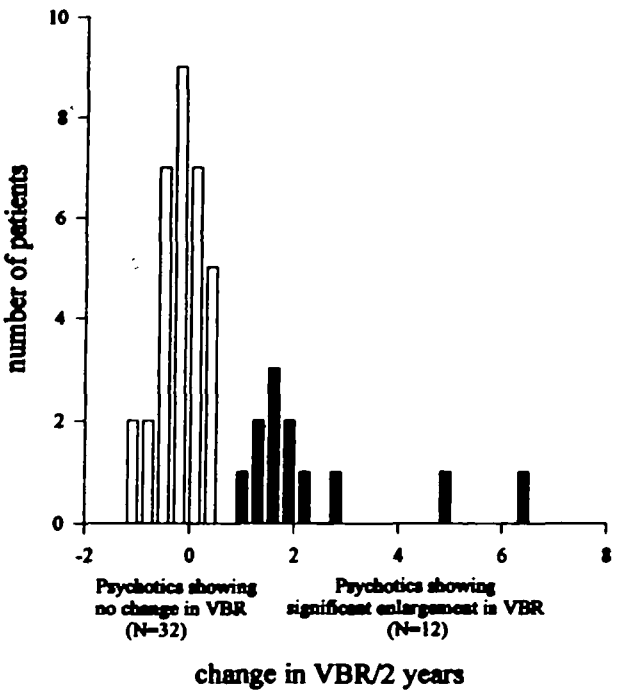
Note.—To assess age-related effects on changes in ventricular size, only studies that included patient age at index scan (rather than mean ages for groups of patients) and that showed an error of the method of less than ± 1 VBR unit were included in the analysis.

ventricular area is derived from scans from which only every 10th slice is projected onto radiographic film for assessment. Thus, it is unlikely that the slice assessed reflects the largest VBR. Furthermore, slight variations in head positioning within the CAT result in larger exposure of lateral ventricles on one side of a slice relative to the other. We first examined those patients in which the VBR appeared to decrease from index to subsequent assessment. Since ventricular volume would physiologically not be expected to decrease in schizophrenia subjects (although ventricular change has been documented in patients with anorexia nervosa [Artman et al. 1985] and in chronic alcoholics undergoing alcohol withdrawal [Carlen et al. 1978]), the decrement in VBR found in schizophrenia subjects should provide an estimate of half the error of the method. Since the other half of the error cannot be estimated from data being assessed for a frank increase in VBR associated with degeneration, it seems most reasonable to estimate the total error by reflecting the decrement both negatively and positively around the 0 (mean error) axis. The estimated 98 percent confidence level of error of the VBR method is then 0 ± 2 standard deviations (SD) of

the mean error; in this study, the error was –0.97 to +0.97. Twelve of the 44 VBRs demonstrated VBR changes outside of the error of the method.

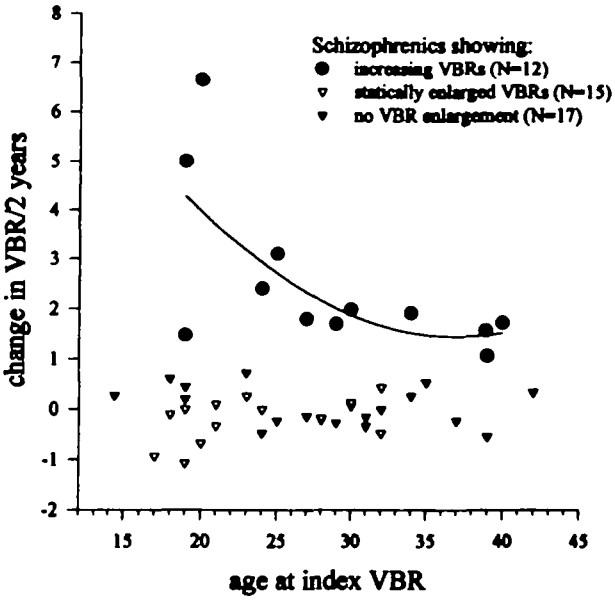
Normality of the VBR change distribution and normality of the VBR distribution with common transformations were assessed by a Lillifores test (*SYSTAT for Windows* 1992). Even with transformations, the distribution of VBR changes differed from normal at the $p < 0.001$ level (figure 1). Cluster analysis with K-means splitting (*SYSTAT for Windows* 1992) estimated two populations of VBR change, with 32 of the 44 schizophrenia subjects (73%) essentially encompassed within the aforementioned error of the method, having a mean ± SD of –0.06 ± 0.41 (range –1.07 to 0.72). A second cluster of patients with VBR change outside the 98 percent confidence level of method error ($n = 10$), contained all but two of the remaining schizophrenia subjects. This cluster had a mean VBR change of 1.85 ± 0.53 (range 1.04 to 3.10). Two additional VBR change outliers had the highest VBR change (mean 6.18 ± 1.14, range 5.04 to 7.32) and were among the three youngest patients (figure 2). The combined second and third (outlier) clusters ($n = 12$, 27%) demonstrated clear evidence of progressive VBR enlargement during the interval between VBR measurements.

Figure 1. Frequency distribution of changes in ventricle-to-brain ratios (VBRs) in schizophrenia patients



Data fails to meet criteria for a normal distribution (Lillifores $p < 0.001$), but fits a bimodal pattern with two outliers (K-means splitting). The data are consistent with two (or perhaps three) distinguishable populations within the syndrome of schizophrenia. An active, progressive enlargement of VBR is shown in the upper groups.

Figure 2. Change in ventricle-to-brain ratio (VBR) in relation to age



All data standardized to a 2-year interval. ● = schizophrenia patients showing increasing VBR throughout young adult life, maximal in teens and early twenties. The curve is the best fit of the data using a second-order regression (*SigmaPlot for Windows* [1986–1994]); ▽ = schizophrenia patients showing enlarged VBR (> 2 SD of age- and sex-matched controls) that are static and are characteristic of a putative early neurodevelopmental psychosis; ▼ = schizophrenia patients without VBR enlargement (characteristic of still other psychoses). Data from Kemali et al. (1989), Woods et al. (1990), Jaskiw et al. (1994), and Vita et al. (1994).

In those schizophrenia patients with increasing ventricular size ($n = 12$), there was a negative correlation between age and change in VBR ($r_p = –0.627$, $p = 0.029$). Even when the two outlying patients were excluded, the remaining patients between the ages of 22 and 41 continued to show a strong negative correlation between VBR and age ($r_p = –0.732$, $p = 0.026$). The greatest change in VBR in these patients appeared to occur in those whose index VBR was performed in their late teens or early twenties (figure 2).

Thirty-two of the 44 (73%) schizophrenia subjects examined in these samples were within the error of the VBR method and showed no evidence of a progressive expansion of VBR. However, 20 of these 32 (62.5%), although showing no progression of ventricular size (figure 2), had index VBRs already greater than 2 SD outside the mean of the controls (mean 2.4 ± 1.1 SD). Continuous expansion of VBR would not be expected in individuals with large static ventricles if the etiology of large VBRs

was related to an early neurodevelopmental abnormality rather than an ongoing neurodegenerative process.

Although several serial studies of ventricular volume using magnetic resonance imaging (MRI) and volumetric techniques are in progress, only two series have been reported in the literature. DeLisi et al. (1992, 1995), following first-break schizophrenia subjects and controls for 4 years, reported more than a 2.4-fold rate of left ventricular expansion (per total brain volume) in schizophrenia subjects as compared with controls, suggesting the presence of an active degenerative process. No difference in the rate of change was found in right ventricular volumes (per total brain volume). Lieberman et al. (1996) found that schizophrenia patients with expansion of ventricles over an 18-month period following a first psychotic episode had a poorer treatment outcome than patients whose ventricles were static. It has recently been reported that elderly people with schizophrenia and a continuing VBR increase have a more severe illness that is not responsive to drugs and is accompanied by premature dementia of a non-Alzheimer's type (Davis 1996, and personal communication December 1995).

Additional Variables That Might Influence Serial VBR Determinations. Treatment with conventional neuroleptics has been shown to result in increased volume of the caudate (Chakos et al. 1994). Such neuroleptic- associated enlargement of the caudate or other structures at the second imaging session and perhaps not the first generally would be expected to result in a decrement in ventricular volume and would work against the findings of ventricular expansion documented herein. While neuroleptic treatment may cause a reduction in volume of certain areas of the brain and concomitant enlargement of ventricular space, the limited available data appear to suggest the opposite.

The possibility that treatment with neuroleptics retards the progression of a neurodegenerative process has been suggested in part as a consequence of data demonstrating a better outcome in patients treated earlier in the course of their illness and treated more consistently with neuroleptics throughout the course of their illness (Wyatt 1991). If true, this would also work against the detection of ventricular expansion in patients treated with neuroleptics.

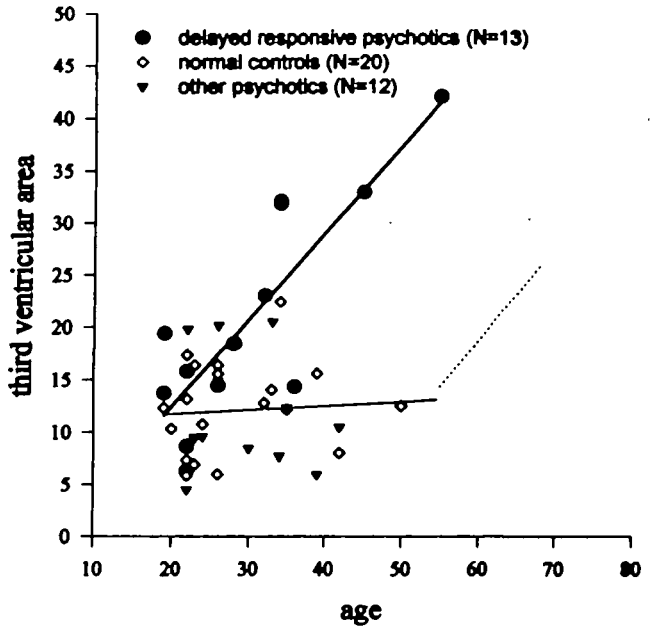
Physiological variations causing a state-associated change in ventricular size have been documented in patients with anorexia nervosa (Artman et al. 1985) and in chronic alcoholics undergoing alcohol withdrawal (Carlen et al. 1978). One might suspect severe dehydration or electrolyte imbalance to be associated with state-related changes in ventricle size. However, if such physiological changes are present in schizophrenia patients they would be expected to be present more often at the initial scan, when the patient was most acutely ill and perhaps "physiologically altered," rather than at the 3-year (or other duration) followup scan. The preponderance of such physiological changes at the time of the first scan followed by partial recovery associated with neuroleptic treatment at the time of the subsequent scans would also result in a mean VBR decrement (rather than expansion) from initial to followup scans.

Cross-Sectional Studies of Brain Ventricles in Schizophrenia Subjects. Cross-sectional reduction of ventricular areas or volumetric data, when correlated with increasing age, can also provide potentially useful information relevant to a premature, ongoing degenerative process. However, such cross-sectional data needs to be interpreted with caution given the many treatment variables and the life differences between schizophrenia and normal comparison groups.

The brain's third ventricular areas can be reliably measured on CAT scans. As with lateral ventricles, third ventricular enlargement is not detectable by CAT scans in normal controls until the sixth or seventh decade of life (Barron et al. 1976). An age-associated increase in third ventricular size measured by CAT scans before the age of 55 in a subgroup of psychotic patients would thus also be consistent with a premature degenerative process.

Schwarzkopf et al. (1990) found age to be correlated with the third VBR in a cohort of schizophrenia subjects between the ages of 18 and 50 ($r_p = 0.54$, $p < 0.05$). Kaplan et al. (1990) reported that third ventricular enlargement in adult psychotic patients is closely related to age, but only in a subgroup of psychotic patients. This latter group of patients showed third ventricular areas that increased with age ($r_p = 0.83$, $p < 0.01$) over a range of 19 to 55 years (figure 3); the slope of this change was significantly greater than the slope of rapidly responsive psychotic patients and controls within the same age range (repeated measures analysis of variance [ANOVA]; $F = 5.71$; $df = 1, 43$; $p = 0.021$). (There was no significant difference between the slopes of normals and of other rapidly responsive psychotic patients [repeated measures ANOVA: $F = 0.175$; $df = 1, 30$; $p = 0.679$].) As noted, in the normal population there is a positive correlation between age and ventricular size (measured by CAT scans) that begins only in the sixth and seventh decades of life (Barron et al. 1976). In this subgroup of psychotic patients, the positive correlation was in effect shifted more than 20 years to the left. Although these psychotic patients could not be symptomatically distinguished from other psychotic patients, they could be identified by their delayed responsiveness to neuroleptic medication (Garver et al. 1988). This subgroup of patients with clear age-related premature increases in third ventricles responded moderately well to neuroleptic medication (with more than a 55% reduction of psychotic

Figure 3. Third ventricular area, delayed responsive psychotics, and age



● = delayed responsive psychotics; ▽ = other drug-responsive psychotics (dopamine and lithium-responsive psychotics); ◇ = normal controls; (. . . . .) = older normal controls. Data from Kaplan et al. (1990) and Barron et al. (1976). Age—3rd ventricular area relationship is shifted more than 20 years to the left in the delayed responsive psychotics.

symptoms) but only after 9 to 45 days (mean of 18.5 ± 10.5 SD) of neuroleptic treatment.

The highly correlated age-ventricular size relationship seen in these delayed-responding psychotic patients throughout the third to fifth decades of life is indicative of a greater than 20-year shift to the left of the age-ventricular size relationship found in normal controls. This study further suggested that it may be possible to identify this "neurodegenerative psychosis" by a specific neuroleptic-response feature: delayed (greater than 8 days) response to conventional antipsychotic drugs during the first decade of the illness (Garver et al. 1988). Ventricular enlargement did not occur in the rapidly responsive dopamine psychotic patients (Kaplan et al. 1990). Others (Weinberger et al. 1980; Luchins et al. 1984; Pandurangi et al. 1989; Frecska et al. 1995; Lieberman et al. 1996) have also reported that patients without ventricular enlargement show a more rapid and better response to antipsychotic medication.

Decreased Volume of Brain Tissues in Schizophrenia. The literature is replete with studies documenting diminished size of structures within the brains of schizophrenia subjects as compared with normal controls. Cortical atrophy has been repeatedly described (Vita et al. 1991; Waddington et al. 1991; Gewirtz et al. 1994) and has been associated with enlarged ventricles (Vita et al. 1988; D'Amato et al. 1992). Similar associations have been noted between ventricular enlargement and both diminished cerebellar size (Coffman and Nasrallah 1985; Nasrallah et al. 1985; Sandyk et al. 1991) and diminished size of the hippocampus (Stevens 1992). However, such studies do not differentiate between progressive degenerating (atrophic) and now-static, early developmental (failure-to-form) processes.

There are, however, two published studies of schizophrenia subjects that relate such differences in brain tissue volumes with age, and one serial study of changes in brain tissue volume over a 4-year period. MRI volumetric examinations of the left posterior temporal gyrus (O'Donnell et al. 1995) and of the cortex (Gewirtz et al. 1994) were highly related to age in some schizophrenia subjects, but not in controls. As noted previously, such cross-sectional data need to be interpreted with caution owing to secondary treatment and life differences between schizophrenia and normal comparison groups. From within-subject serial volumetric MRI examinations (with age-matched controls), DeLisi et al. (1995) reported a significantly increased rate of atrophy in the left temporal lobe and in both left and right cerebral hemispheres of schizophrenia subjects. Reanalysis of the rate of volume change for both right and left hemispheres found a nonnormal distribution in schizophrenia subjects (Kolmogorov-Smirnov one-sample test using a standard normal distribution, $p = 0.001$), even after the exclusion of an outlier. These data were also consistent with a multimodal distribution of hemispheric atrophy, the upper mode consistent with an ongoing, active neurodegenerative process.

Progressive Resistance to Neuroleptic Treatment. Upon readmission for a subsequent psychotic episode, five out of five of our delayed-responding psychotic patients required additional days of neuroleptic treatment to achieve a response similar to that found during the previous episode (Garver et al. 1988). Other studies have revealed that with each psychotic episode, some schizophrenia subjects become progressively resistant to antipsychotic drugs, with further delays in response times, a progressively poorer antipsychotic outcome (Wyatt 1991; Lieberman et al. 1993, 1996; Loebel et al. 1995), and perhaps eventual schizophrenic dementia (Purohit et al. 1993). Such patients have difficulty regaining previous levels of functioning and show evidence of a progressively deteriorating illness. Elderly schizophrenia subjects with such a debilitating nonresponsive schizophrenic illness have recently been reported to display expanding ventricular volumes (Davis 1996, and personal communication December 1995).

These response patterns, seen in some schizophrenia subjects, again suggest a neurodegenerative process.

Neurodegeneration and Electrophysiological Changes. The P300 cortical event-related potential (ERP) elicited by the "odd ball stimulus paradigm" is generated in the posterior temporal gyrus. Latency of the P300 cortical ERP is known to increase during normal aging and is further accelerated in individuals with such neurodegenerative disorders as dementia, Alzheimer's disease, multiple sclerosis, Huntington's chorea, and Parkinson's disease (O'Donnell et al. 1995).

O'Donnell et al. (1995) found that some schizophrenia subjects also show age-associated increased latency of the P300. Though some schizophrenia subjects had P300 latencies similar to that of normal controls, one schizophrenia subgroup manifested significantly longer age-related latencies that appeared to be inversely correlated to the size of the posterior temporal gyrus. In comparison with age-matched controls, this schizophrenia subgroup exhibited an age-related shift to the left of the P300. This finding parallels the observation of the more than 20-year shift to the left reported in third ventricle-age relationships in the subgroup of psychotic patients who manifest the delayed antipsychotic response to neuroleptic drugs (Kaplan et al. 1990). This is also consistent with the findings of changes in the ratio of synthesis and breakdown of membrane phospholipids described by magnetic resonance spectroscopy (MRS) in some schizophrenia patients (see below). As noted previously, cross-sectional studies relating age to ventricular size, temporal lobe volume, or P300 must always be interpreted particularly cautiously given the many treatment-related and life-style differences between some patients with schizophrenia and comparison groups.

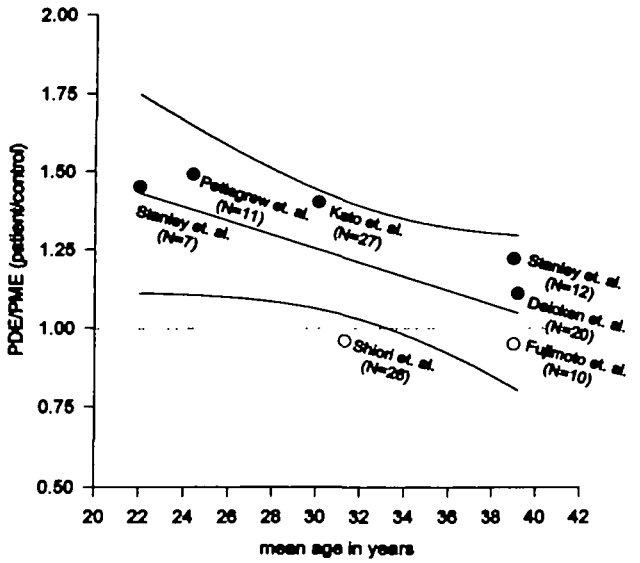
Excess Products of Membrane Degeneration in Some Schizophrenia Subjects. MRS may be able to identify patients with an active, ongoing neurodegenerative process from the larger group of schizophrenias. Phosphorus MRS (^{31}P–MRS) is a noninvasive tool that permits the quantitation of select substances related to phosphorus and phospholipid metabolism in vivo. It can be used to quantify critical phospholipids, which are the primary constituents of cellular membranes. In particular, the synthesis and breakdown of membrane phospholipids can be estimated by quantification of the phospholipid membrane building blocks versus the breakdown products of membrane metabolism. Phosphomonoesters (PMEs), such as phosphoethanolamine and phosphocholine, are the precursors of membrane phospholipids. The phosphodiesters (PDEs), including glycerol 3-phosphoethanolamine and glycerol 3-phosphocholine, are the breakdown products of membrane phospholipid metabolism. An excess of breakdown products (PDE) as compared with building blocks (PME), resulting in an elevated PDE/PME ratio, is indicative of ongoing tissue degeneration (Pettegrew et al. 1993), as opposed to tissue growth or equilibrium.

The PDE/PME ratio in the frontal cortex of schizophrenia patients from seven age-specified cohorts and their age-matched controls has been described in the recent literature (Pettegrew et al. 1991; Fujimoto et al. 1992; Deicken et al. 1994; Shioiri et al. 1994; Stanley et al. 1994 [two cohorts]; Kato et al. 1995). The PDE/PME of each schizophrenia cohort was standardized for age and sex by dividing each cohort's ratio by the PDE/PME of the investigator's own age-matched controls. If a schizophrenia subject had excess PDE or a relative deficiency of PME as compared with controls, the ratio in that schizophrenia cohort would be greater than 1.0. Each of the cohorts was assumed to be composed of a mixture of degenerative psychotic patients and other nondegenerative psychotic patients. In such a mixture, the "signal" of the degenerative process, present in only a subgroup of the psychotic patients, must be sufficiently strong to be detected over the "noise" generated by the remaining nondegenerative psychotic patients.

Mean age-corrected PDE/PME ratios were significantly elevated in the three youngest schizophrenia cohorts investigated (Pettegrew et al. 1991; Stanley et al. 1994; Kato et al. 1995) (figure 4). These were cohorts with a mean age of 22 to 30 years—similar to the age of patients showing maximum changes in VBR (figure 2). Thus, the PDE/PME signal from a degenerative group of psychotic patients within a presumed mixture of younger schizophrenia subjects was sufficiently strong to raise the mean cohort PDE/PME as compared with age-matched controls. Within the mixture of psychotic patients aged 31 years and older, there was still a sufficient signal from degenerative psychotic patients to provide PDE/PME ratios in excess of the age-matched controls in two of the four older cohorts, similar to the continuing but smaller increases in VBR in the subgroup of degenerative psychotic patients seen in figure 2.

Recently, Stanley et al. (1995) have characterized the PME building blocks as being diminished throughout the course of schizophrenia, with a particular increase in PDEs during the early part of the illness. Diminished PMEs in some schizophrenia subjects throughout the course of the illness suggest impairment of the usual ongoing process of cell repair and regeneration. Since central nervous system (CNS) tissues, like those in the periphery, are constantly undergoing programmed cell death (apoptosis; see below), the decrement of regenera-

Figure 4. Phosphodiester (PDE) and phosphomonoester (PME) ratios (PDE/PME) in the frontal cortex in age-identified cohorts of syndromally identified schizophrenia patients



Each cohort corrected for age and sex by dividing PDE/PME ratios of patients by those of age- and sex-matched controls. Displayed ratios greater than 1.0 (●) indicate increase in PDE/PME ratios; (○) indicates nonsignificant decrease in PDE/PME ratios. Data from Pettegrew et al. (1991), Fujimoto et al. (1992), Deicken et al. (1994), Shioiri et al. (1994), Stanley et al. (1995) (two cohorts), and Kato et al. (1995).

tion and repair, as reflected by a paucity of PMEs, results in a progressive, chronic net loss of brain tissue. An increase in age-associated neuropil loss during the early twenties in some schizophrenia subjects may be reflected by the early temporary increase in PDEs.

The data from the age-corrected ^{31}P–MRS studies, from a putative mixture of neurodegenerative and other psychoses, are strikingly parallel to the aforementioned changes in VBR in some of the schizophrenia subjects (figure 1), with higher PDE/PMEs and a greater rate of ventricular expansion in the early twenties followed by evidence of sustained, but less elevated ratios or ventricular volume changes. The data are also consistent with the age-associated increase in third ventricular areas described in the delayed responsive psychosis (figure 3). These findings provide very strong support for the concept of acute tissue loss in the late teens and early twenties, and ongoing failure of neuropil maintenance in one of the disorders that make up the schizophrenia syndrome.

Summary of Studies Supporting a Neurodegenerative Psychosis. The evidence presented here indicates that schizophrenia is not a homogeneous disorder. Rather, these studies reveal heterogeneous schizophrenia cohorts. Some of these schizophrenia subjects have cerebral ventricles that enlarge over time; some show a more than 20-year shift to the left of the usual age-related third ventricular area relationship accompanied by a delayed neuroleptic response. Some appear to show a similar age-related decrement in temporal lobe volume. Some evidence progressive loss of cerebral cortical and temporal lobe volume. One schizophrenia subgroup demonstrates increased latency of the P300. Some schizophrenia subjects show age-related increases in PDE/PME ratios. Some appear to experience progressive difficulty in responding to neuroleptics during repeated hospitalizations, with the eventual development of a severely debilitating "dementia praecox."

The most parsimonious explanation for these phenomena would be a single degenerative disorder, rather than many. Proof that these subgroups indeed represent schizophrenia subjects with a single progressive neurodegenerative disorder awaits comprehensive studies that would confirm, in the same group of patients, progressive ventricular enlargement, progressive cerebral atrophy, higher PDE/PME ratios, delayed P300s, and a progressively delayed treatment response.

Possible Etiologies for a Neurodegenerative Schizophrenia

The existence of a neurodegenerative subtype of schizophrenia raises other issues. The cause of the degenerative process that appears to occur in the brains of some schizophrenia subjects remains unknown. There are, however, substantial leads, and explorations concerning the nature of this process are already ongoing. As the etiology of this process becomes better understood, it is likely that new therapeutic approaches will be directed more specifically toward the causes of the neurodegenerative process that produces such psychiatric morbidity. A very important lead focuses on the processes of neuropil turnover: tissue maintenance and elimination. Apoptosis occurs when an intracellular, genetically encoded death program is released from inhibition. A variety of neurotrophins present in a cellular environment ward off this genetically induced apoptotic cascade. Certain forms of free-radical toxicity also appear to be associated with the release of apoptosis programs.

Degeneration and Apoptosis. Brain tissue can degenerate by either necrosis or apoptosis. Necrosis follows injury and consists of cellular swelling, lysis, and the subsequent spilling of cellular contents into the extracellular space. An

inflammatory response ensues, including glial proliferation. During apoptosis, nucleus and cytoplasm condense and fragment, with the fragments being rapidly phagocytized by neighboring cells or macrophages. No inflammatory process or gliosis occurs. Even large-scale apoptosis is often histologically inconspicuous (Kerr et al. 1972).

In the embryonic development of the CNS, apoptosis plays a critical role in determining which cells and neuropil (axons, dendrites) will survive. Cells that project onto appropriate target cells and receive neurotrophins from the target cells are sustained. Inappropriate projections onto cells that cannot provide the necessary neurotrophic factors result in programmed elimination (Cowan et al. 1984). It has been estimated that 50 percent of neurons and their projections once present in the CNS have disappeared via apoptosis by early adulthood (Raff et al. 1993).

However, apoptosis does not cease upon the completion of neurodevelopment or with the termination of the normal synaptic pruning of late adolescence. Rather, apoptosis continues throughout the life of the organism (Barde 1994). Cells and neuropil are constantly eliminated via apoptosis, and neuropil is often replenished by regeneration. When regeneration and apoptosis are in equilibrium, tissues are stable. When apoptosis is accelerated or regeneration is reduced, tissue loss is apparent.

Techniques that quantify degeneration and regeneration may be particularly useful in studying the parameters associated with neurodegeneration. One such technique is ^{31}P–MRS. As noted earlier, a relative decrement in PMEs is associated with a partial failure in the process of maintenance and regeneration. Excess PDEs may be associated with an elevated rate of cellular or neuropil death. The elevated PDE/PME ratio and progressive decrease of brain substance in some schizophrenia subjects can therefore be associated with an acute apoptotic process in the late teens or early twenties (accompanied by elevated PDEs), followed by a continuous partial failure of maintenance and regeneration (accompanied by chronic diminished PMEs). Together, the processes may result in an initially acute, then slow chronic loss of brain volume and consequent increase in ventricular size.

Pathological Extension of Synaptic Pruning and Schizophrenia. A considerable amount of literature has suggested that schizophrenia may be, in part, a disorder of late neurodevelopment gone awry. Later phases of neurodevelopment (during and following puberty) are associated with the pruning of redundant, juvenile synapses and cellular disappearance, both of which then stabilize during normal adult life (Huttenlocher 1979). Such pruning has been reported to be associated with decreased oxygen use, decreased total sleep duration, and increased latency of ERPs (Feinberg 1982/83). Some adults with schizophrenia show an exaggeration of exactly these physiological markers of adolescent pruning: decreased frontal lobe metabolism, increasing deficits in slow-wave sleep, and delayed latency or reduced amplitude of ERPs (Keshavan et al. 1994; O'Donnell et al. 1995). These features, coupled with a frequent onset of psychoses during late adolescence, may be evidence of a pathological extension of the adolescent pruning process into adulthood.

Pathological extension of pruning is consistent with a continued apoptotic process associated with increased PDEs on ^{31}P–MRS in some schizophrenia subjects in their early twenties. While the factors underlying the control of normal synaptic pruning and its potential pathological extension are poorly understood, extended pruning and elevations of PDEs may be a result of apoptosis occasioned by the failure of protective neurotrophins.

Neurotrophic Factors and Schizophrenic Neurodegeneration. Neurotrophic factors (such as nerve growth factor [NGF], brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4/5, and others), are produced by a variety of CNS cells. They inhibit the spontaneous initiation of death programs as they interact with neuronal membrane proteins (Barde 1994). Perez-Polo et al. (1978) reported that the cerebrospinal fluid of some schizophrenia subjects contains a paucity of NGF as determined by immunoassay (30% of normals) and bioassay (5% of normals). Bersani et al. (1996) found significantly lower levels of NGF in the plasma in schizophrenia subjects (both drug free and neuroleptic treated) compared with normal controls. A decrement of one or more NGFs in adults with schizophrenia may also lead to apoptotic degeneration.

Free Radical and Detergent-Induced Cellular Injury in Schizophrenia. Free radical injury is accompanied by the appearance of reactive oxygen radicals (RORs) that are formed as a consequence of tissue oxidation. Recent evidence has implicated free radicals as triggers of some forms of apoptosis (Wood and Youle 1994). RORs are generated as a consequence of a number of metabolic processes within the CNS. Many of the processes feed back upon themselves, producing an ever-renewing cascade of fresh oxidation and ROR products.

Unsaturated fatty acids, enriched in the brain, are especially susceptible to oxidation. The interaction of RORs with membrane unsaturates produces a range of products, including free fatty acids and lipid peroxidases. Lipid peroxidases continue to degrade more unsaturated fatty acids autocatalytically (Cotran et al. 1989). Released free fatty acids themselves have detergent properties, altering membrane fluidity and integrity, uncoupling

oxidative phosphorylation and ion balance (Anderson and Thomas 1994). Certain unsaturated fatty acids (especially 20- and 22-carbon) are deficient in the plasma and red blood cell membranes of some schizophrenia subjects (Kaiya et al. 1991; Yao et al. 1994), and their concentrations appear to be bimodally distributed (Glen et al. 1994), suggesting that a subgroup of schizophrenia patients may be particularly susceptible to free radical oxidation of membrane unsaturates.

Phospholipase A_2 (PLA_2) activity has been found to be elevated in the plasma (Gattaz et al. 1987, 1990; Albers et al. 1993; Noponen et al. 1993) and platelets (Gattaz et al. 1995) of some schizophrenia patients. PLA_2 is an enzyme that catalyzes the hydrolysis of membrane phospholipids to release free fatty acids and other cytotoxic products, such as lysophosphatidylcholine (Anderson and Thomas 1994). Such cytotoxins further accelerate the breakdown of membrane phospholipids. Increased lysophosphatidylcholine has been described in the platelets of some schizophrenia subjects (Pangerl et al. 1992), and excess phospholipid breakdown products have been found in post-mortem studies of the frontal lobes of some schizophrenia subjects (Horrobin et al. 1991).

Studies of peroxidases, ROR-scavenging enzymes, antioxidants, and products of such lipid peroxidation have been reported in schizophrenia. Increased plasma lipid peroxidases have been found in some schizophrenia subjects (Prilipko 1984). A deficiency of the scavenger enzyme superoxide dismutase was reported in the red blood cells of some first-episode, drug-naive schizophrenia subjects (Mukherjee et al. 1994). An association between a deficiency in the scavenger enzyme glutathione peroxidase and an excess of an end product of lipid peroxidation, thiobarbituric-acid-reactive malonyldialdehyde products has been reported in the plasma of some people with schizophrenia (Mahadik et al. 1995; Scheffer et al. 1995).

The notion that a neurodegenerative psychosis is associated with an apoptotic process triggered by free radical oxidation of susceptible unsaturated phospholipids awaits further confirmatory studies. Such studies will need to examine simultaneously, in the same subjects, changes in ventricular size, alterations in PDEs (and perhaps PMEs), membrane phospholipid unsaturation, lipid peroxidases, membrane-derived cytotoxins, and PLA_2 activity.

Glutamate-Associated Neurodegeneration. The amino acid neurotransmitter glutamate is neurotoxic at high tissue concentrations (Rothman and Olney 1986). Excess glutamate activity is associated with neurodegenerative processes of several CNS disorders, including Huntington's disease (Shoulson 1983) and Parkinson's disease (Klockgether and Turski 1993), as well as with secondary excitotoxic degeneration following stroke (Simon et al. 1984) or spinal cord injury (Collins and Olney 1982). Parkinson's-associated degeneration of the striatal projection neurons, accompanied by impaired dopamine activity, bears all the characteristics of glutamate-induced apoptosis. Such glutamate-induced striatal apoptosis can be prevented in animal models of Parkinson's disease by administering glutamate antagonists (or by interrupting cortical-striatal glutamate tracts) (Mitchell et al. 1994).

Despite intriguing leads from animal studies (Olney and Farber 1995), only limited evidence supports glutamate-induced neurotoxicity in schizophrenia. Indirect evidence comes from observations that neurons, presumably innervated by glutamate, have decreased uptake sites for their primary neurotransmitters and may therefore be partially destroyed by the excitotoxic effects of glutamate. There are decreased uptake sites for gamma-aminobutyric acid (GABA) on GABA neurons presumably once innervated by glutamate neurons in the putamen (Simpson et al. 1992) and reduced dopamine re-uptake sites on dopamine neurons in the prefrontal cortex (Hitri et al. 1995). Hitri et al. (1995) found that the decrease in dopamine transport activity is inversely related to age in people with schizophrenia, whereas age- and sex-matched controls showed no such age-associated reduction over an age span of 19 to 77 years. The Hitri study documents an age-related, progressive decrease in dopamine cells (if the dopamine transporter is a reliable marker for the quantity of dopamine neurons). The only other known evidence of possible transsynaptic degeneration putatively associated with glutamate hyperactivity is the observation of decreased glutamate binding in the medial temporal cortex of schizophrenia subjects (Kerwin et al. 1988; Deakin et al. 1989).

Conclusions

Converging evidence from a variety of lines of research suggests that nested among the group of syndromal schizophrenias is an etiologically distinct form of psychosis that provides evidence of progressive premature atrophy of brain substance, increasing cerebral ventricular size, failure to maintain cellular membrane phospholipids, premature neurophysiological changes (P300), and delayed response to neuroleptic treatment. Although presenting with hallucinations, delusions, and thought disorders similar to those of other people with schizophrenia, these psychotic patients appear to suffer from a neurodegenerative disorder. Unlike other forms of psychosis, there is no evidence that this disorder is associated with a functionally hyperactive dopamine system (Garver et al. 1997) or with early neurodevelopmental pathology.

Identification of such a degenerative schizophrenia may be possible even before the first psychotic episode through MRS studies of ratios of phospholipid degradative products to precursors in the brains of psychotic patients: Keshavan et al. (1991) found an elevated PDE/PME ratio in a "control" patient who developed symptoms of schizophrenia 2 years later. However, the specificity and sensitivity of this MRS method for detecting a degenerative psychotic disorder has not yet been reported in relation to the "gold standard" of progressive, increasing ventricular size measured with serial CAT or MRS examinations.

To date, the best clinical correlate of the degenerative process may be a delayed antipsychotic response to conventional antipsychotic drugs (Kaplan et al. 1990), followed by further delays in responsiveness during each subsequent episode of treatment (Lieberman et al. 1993, 1996) and perhaps the development of a premature dementing process (Purohit et al. 1993; Davis 1996, and personal communication December 1995). It may be that the initial and early progressive delays in response represent the early period of deterioration described by Breier et al. (1991) in the first decade of the active schizophrenic process (usually beginning during the late teens to early twenties). According to Breier's data, after a rapid progression, the disease progresses less rapidly, if at all, during an intermediate period in the third and fourth decades, as perhaps reflected by slower changes in VBRs (figure 2) and a relative decrease, during middle age, of the highly elevated PDE/PME ratios found in the twenties (figure 4).

Using delayed antipsychotic response as a marker to identify the group of patients with a neurodegenerative process, we have previously described a 10.6 percent risk in first-degree relatives for developing a similar psychotic process, with a similar poor prognosis (Sautter et al. 1993). Such putative familiality of the neurodegenerative psychosis should be established using the gold standard of premature, progressive increase in ventricular size in multiple pedigree members of neurodegenerative probands. The possibility of identifying a susceptibility site or sites within the human genome for the degenerative psychosis is also intriguing. One would anticipate that the linkage sites for the neurodegenerative psychosis might be different from the sites for other familial (genetic) forms of schizophrenia. Such differences in genomic susceptibility sites in the neurodegenerative, neurodevelopmental, and dopamine psychosis pedigrees (Garver et al. 1997) would confirm the genetic heterogeneity of the schizophrenias (Garver et al. 1989). Moreover, one or more linkage sites limited to probands and pedigrees with a neurodegenerative process would be the ultimate validator for the separation of such a degenerative psychosis from the bulk of the schizophrenias.

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Acknowledgments

This research was supported in part by grant MH-42666 to Dr. Garver from the National Institute of Mental Health, a Department of Veterans Affairs Merit Review to Dr. Garver, and the Southwestern Medical Center John Schermerhorn Psychiatric Fund.

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